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A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies

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Abstract

Invasive candidiasis is a life-threatening infection in patients with haematological malignancies. The objective of our study was to determine the incidence, microbiological characteristics and clinical outcome of candidaemia among hospitalized adult patients with haematological malignancies. This is a population-based, prospective, multicentre study of patients ≥18 years admitted to haematology and/or haematopoietic stem cell transplantation units of nine tertiary care Greek hospitals from January 2009 through to February 2012. Within this cohort, we conducted a nested case-control study to determine the risk factors for candidaemia. Stepwise logistic regression was used to identify independent predictors of 28-day mortality. Candidaemia was detected in 40 of 27 864 patients with haematological malignancies vs. 967 of 1 158 018 non-haematology patients for an incidence of 1.4 cases/1000 admissions vs. 0.83/1000 respectively ($p < 0.001$). Candidaemia was caused predominantly (35/40, 87.5%) by non-*Candida albicans* species, particularly *Candida parapsilosis* (20/40, 50%). *In vitro* resistance to at least one antifungal agent was observed in 27% of *Candida* isolates. Twenty-one patients (53%) developed breakthrough candidaemia while receiving antifungal agents. Central venous catheters, hypogammaglobulinaemia and a high APACHE II score were independent risk factors for the development of candidaemia. Crude mortality at day 28 was greater in those with candidaemia than in control cases (18/40 (45%) vs. 9/80 (11%); $p < 0.0001$). In conclusion, despite antifungal prophylaxis, candidaemia is a relatively frequent infection associated with high mortality caused by non-*C. albicans* spp., especially *C. parapsilosis*. Central venous catheters and hypogammaglobulinaemia are independent risk factors for candidaemia that provide potential targets for improving the outcome.

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Introduction

Invasive candidiasis is associated usually with excess morbidity and mortality, longer hospital stays and higher hospital costs in patients with haematological malignancies [1–5]. Candidaemia, the most common form of invasive candidiasis, is associated with unacceptably high mortality rates, reaching 40% among haematology patients, despite the introduction of newer antifungal agents [3]. Therefore, information on the incidence, epidemiology, risk factors and outcome of this deadly infection is of paramount importance in the care of patients with haematological malignancies.

Most estimates of incidence and epidemiology of candidaemia among patients with haematological malignancies have been derived from studies conducted in single institutions or

from retrospective surveys focusing on specific *Candida* species. Thus, institution-specific limitations, such as local epidemiology, patient populations, antineoplastic protocols, available facilities, infection control policies, prophylaxis and treatment practices, or even environmental exposures, prohibit generalization of epidemiological findings across multiple centres. Retrospective assessment of the incidence of candidaemia with use of microbiology or pharmacy databases and discharge or death records has major limitations that could lead to inaccurate estimates [6].

Prospective surveillance studies and/or nationwide registries of candidaemia and/or invasive fungal infections include subpopulations of candidaemic haematology patients, providing additional epidemiological information [7,8]. However, these studies do not focus specifically on haematology patients with candidaemia. Clinical trials and comparative studies on treatment of candidaemia usually include only a paucity of neutropenic patients with haematological malignancies.

The aim of our study, therefore, was to determine prospectively the incidence, microbiological characteristics, susceptibility patterns and clinical outcome of candidaemia among hospitalized adult patients with haematological malignancies. To that end, a prospective, multicentre, cohort study was conducted in nine tertiary care Greek hospitals with haematology and/or haematopoietic stem cell transplantation (HSCT) units. Within this prospective cohort, we conducted a nested case-control study to determine the risk factors for candidaemia. Microbiology data on the distribution of *Candida* species and their resistance patterns were also collected and analysed. Finally, the epidemiology of candidaemia among haematology patients was compared with that of non-haematology patients admitted to the same hospitals during the study period.

Design and Methods

Study population

We conducted a population-based, prospective, multicentre, study of all patients ≥18 years of age admitted to haematology and/or HSCT units of nine tertiary care Greek hospitals during the period from 1 January 2009 through to 28 February 2012. All patients admitted to the haematology units and to all other non-haematology departments of the participating hospitals were identified using both hospital and unit-specific databases.

Definition of case patients and selection of control patients

Candidaemia in a patient with haematological malignancy was defined according to published guidelines [9]. Case patients were identified by the primary physicians at the participating haematology units. If multiple, distinct episodes of candidaemia occurred in the same patient during the study period, then only the first episode was included in our analysis.

Control patients were selected by the use of unit-specific patient admission databases. In order to match control patients to case patients with respect to time at risk of developing candidaemia (i.e. length of stay in the same haematology unit) we selected as control patients the two subjects with haematological malignancies who were admitted subsequent to the case of candidaemia and did not develop candidaemia during their hospitalization. The index date was considered as the day of positive blood culture for the case patient and the corresponding day in the haematology unit for the two matched controls. Candidaemia was defined by the caring physician as catheter related: (i) when there was no other apparent source of the infection; (ii) when the same *Candida* species was isolated from both peripheral blood and blood drawn from the lumen of the central venous catheter (CVC) and/or from catheter-tip culture; and (iii) if the patient had prolonged candidaemia that quickly resolved after removing the CVC. The CVC was considered to be removed if this procedure was performed during the first 3 days following the first blood culture positive for *Candida* infection. The terms of *de novo*, breakthrough candidaemia, neutropenia and *Candida*-related mortality were defined as described previously [10].

Data collection

Data collection was performed by primary physicians at the participating haematology units. On the index day, a standardized form was used to record the following data: patient demographics; type of underlying haematological malignancy; history of prior chemotherapy and/or HSCT; depth of neutropenia (absolute neutrophil count (ANC) <500, ANC <100); duration of, and recovery from, neutropenia; presence of CVC and subsequent removal; use of corticosteroids within the previous 4 weeks; administration of total parenteral nutrition; presence of diabetes mellitus or renal failure; hypogammaglobulinaemia; use of growth factors; admission to the intensive care unit (ICU); intercurrent bacterial infection; and prior or concurrent use of antifungal agents and/or broad spectrum antibiotics. The Acute Physiology and Chronic Health Evaluation (APACHE II) score, Eastern Cooperative Oncology Group (ECOG) performance scale and Glasgow Coma Scale (GCS) scores were calculated at the onset of candidaemia.

The antifungal agents used for the treatment of candidaemia were recorded, and the patients were evaluated at days 7, 14 and 28 for evidence of disease, clinical and/or mycological response and outcome. Cases of candidaemia in non-haematology

patients of the participating hospitals, during the study period, were identified through records of the microbiology laboratories. Institutional review boards of all participating centres approved the study protocol.

Microbiology studies

For case patients with candidaemia, information regarding species of *Candida* was collected. Species identification was performed in the microbiology laboratory of each participating centre, by using standard methods. In order to eliminate variation due to different techniques, methods and expertise among the nine reporting microbiology laboratories, we collected the available isolates ($n = 30$) after the conclusion of the study and performed susceptibility testing in the same laboratory by the same methods. Minimum inhibitory concentrations (MICs) were determined by using the most recent interpretive breakpoints adopted by the Clinical and Laboratory Standards Institute (CLSI) and published in document M27-S4 [11].

Statistical analysis

Categorical variables were compared using Fisher's exact test and continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test. Survival was plotted by Kaplan–Meier analysis and analysed by log-rank test. Logistic regression was used to identify variables independently associated with the development of candidaemia. A separate logistic regression model was used to identify the risk factors for mortality. All variables associated with the outcome of interest in the bivariate analysis ($p < 0.1$) were included at model entry, and a stepwise approach was used to identify independent predictors of 30-day mortality. Variables were retained in the final model if the p value was 0.05. All calculations were performed with SPSS version 16 (SPSS, Chicago, IL, USA).

Results

Incidence of candidaemia, demographics and clinical characteristics of case patients and controls

During the study period, 27 864 adult patients with haematological malignancy and 1 158 018 patients without haematological malignancy were admitted to nine participating hospitals. A total of 40 haematology patients and 967 non-haematology patients were identified with candidaemia. The incidence of candidaemia was 1.4 cases per 1000 admissions for patients with haematological malignancy vs. 0.83 cases per 1000 admissions in non-haematology patients ($p < 0.001$).

Risk factors for candidaemia among patients with haematological malignancies

A total of 80 control patients were selected. Table 1 displays clinical and demographic characteristics of candidaemia cases and controls. On univariate analysis, case patients were more likely than control patients to have a CVC in place, diabetes mellitus, neutropenia, prior use of corticosteroids, hypogammaglobulinaemia, history of HSCT and a higher APACHE II score (Table 1). Multivariate analysis showed that CVC, hypogammaglobulinaemia and an elevated APACHE II score were independent risk factors for the development of candidaemia (Table 1).

Distribution of *Candida* species and epidemiological characteristics among patients with candidaemia

Most infections (35, 87.5%) were caused by non-*Candida albicans* species. The distribution of *Candida* species in decreasing order was *Candida parapsilosis* (20, 50%), *Candida tropicalis* (6, 15%), *C. albicans* (5, 12.5%), *Candida glabrata* (4, 10%), *Candida guilliermondii* (2, 5%), and one each of other species (Table 2).

Twenty-one patients (53%) developed breakthrough candidaemia, while receiving antifungal prophylaxis (9/21, 43%) or empirical treatment (12/21, 57%). Prior antifungal exposure included fluconazole (6/21, 29%), liposomal amphotericin B (5/21, 24%), posaconazole (4/21, 19%) and echinocandin (2/21, 10%), while four patients received more than one antifungal agent. The most common species recovered from breakthrough cases was *C. parapsilosis* (62%). Twenty (50%) cases of candidaemia were considered as CVC-related, with *C. parapsilosis* being the most common species recovered (55%).

Of the 967 episodes of candidaemia in non-haematology patients, species identification was performed in 752 isolates. The most frequently reported species were *C. albicans* (392/752, 52%), *C. parapsilosis* (275/752, 36.5%) and *C. tropicalis* (85/752, 11.3%).

Non-*C. albicans* candidaemia was significantly more frequent among haematology patients (35/40, 87%) compared with non-haematology patients (360/752, 48%) ($p < 0.0001$). Candidaemia caused by *C. parapsilosis* also occurred more frequently in patients with haematological malignancies (20/40, 50%) than in non-haematology patients (275/752, 36.5%) (p 0.09).

Susceptibility patterns of *Candida* spp. isolated from patients with haematological malignancies

Of the 30 *Candida* isolates tested, eight (27%) were resistant to at least one antifungal agent. For nine (30%) other isolates, susceptibility was characterized as susceptible-dose dependent (SDD) or intermediate to at least one antifungal agent. Resistance was more common for itraconazole (four isolates

TABLE 1. Demographics of the study population and risk factors for candidaemia in patients with haematological malignancy

Characteristic	Case patients (*n* = 40)	Control patients (*n* = 80)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Median age, years (range)	58 (19, 89)	55 (16, 89)	1.01 (0.99, 1.04)	
Sex, n (%)			1.28 (0.6, 2.75)	
Male	19 (48%)	43 (54%)		
Female	21 (52%)	37 (46%)		
Haematological malignancy, n (%)			1.17 (0.54, 1.26)	
Leukaemia/myelodysplastic syndrome	24 (60%)	51 (64%)		
Lymphoma/multiple myeloma	16 (40%)	29 (36%)		
Surgical procedure (abdomen)	0	1 (1%)	–	
Diabetes mellitus	8 (20%)	10 (12%)	1.75 (0.63, 1.85)	
Presence of CVC	31 (78%)	25 (31%)	7.58 (3.14, 18.27)	5.99 (2.36, 15.22)
TPN	2 (5%)	0		
Hypogammaglobulinaemia, n (%)	20 (50%)	18 (23%)	3.39 (1.50, 7.64)	3.39 (1.35, 8.54)
Neutropenia, n (%)	29 (73%)	52 (65%)	1.42 (0.62, 3.26)	
Profound neutropenia (<100/mL), n (%)	17 (59%)	28 (56%)	1.11 (0.44, 2.81)	
Use of growth factors, n (%)	27 (68%)	48 (60%)	1.38 (0.62, 3.08)	
Systemic corticosteroids within 4 weeks before onset, *n* (%)	21 (52%)	35 (44%)	1.42 (0.66, 3.04)	
Stem cell transplantation, *n* (%)	11 (28%)	19 (24%)	1.22 (0.51, 1.89)	
Autologous	3	11		
Allogeneic	8	8		
Graft-vs.-host disease	3	2		
APACHE II score at onset, *n* (%)			4.33 (1.62, 11.61)	3.06 (1.02, 9.20)
≥20	13 (33%)	8 (10%)		
<20	27 (67%)	72 (90%)		
Median APACHE II score (range)	17.5 (9, 32)	14 (4, 27)		

OR, odds ratio; CVC, central venous catheter.

TABLE 2. Microbiology, treatment and outcome of patients with Candidaemia and haematological malignancies

Microbiology and treatment parameter	*n* = 40 cases
Causes of candidaemia	
Organisms	
Candida parapsilosis	20 (50%)
Candida tropicalis	6 (15%)
Candida albicans	5 (12.5%)
Candida glabrata	4 (10%)
Candida guilliermondii	2 (5%)
Other *Candida* species[a]	3 (7.5%)
Breakthrough candidaemia[b]	21 (53%)
CVC-related candidaemia[b]	20 (50%)
Treatment	
Initiation of antifungal treatment in patients not receiving antifungal agents	18 (45%)
Switching to another class of antifungals in cases of breakthrough infection	7 (17.5%)
Addition of antifungal agents to the existing regimen	8 (20%)
Continuation of the initial antifungal therapy	6 (15%)
Removal of CVC (<72 h)	11 (27.5%)
Median duration of treatment (days, range)	12 (1–81)
Outcome	
Clinical response (day 7)	14 (35%)
Mycological response (day 7)	19 (47.5%)
Overall response (day 28)	22 (55%)
Crude mortality (day 28)	18 (45%)
Susceptibility to antifungal agents[c]	
C. parapsilosis	11/13 (84.6%)
C. tropicalis	4/5 (80%)
C. albicans	4/4 (100%)
C. glabrata	2/4 (50%)

[a]*Candida krusei*, *Candida dubliniensis*, *Candida kefyr*.
[b]According to published definitions [Antoniadou *et al.*10]
[c]Isolates susceptible to all antifungal agents (excluding itraconazole). Data from 30 available isolates.

were resistant and eight SDD). If itraconazole is excluded from the analysis, then 17/30 (57%) isolates were susceptible to all antifungal agents. Resistance to antifungal agents was observed only among non-*C. albicans* species. Among the 13 available isolates of *C. parapsilosis*, one was resistant and three had intermediate susceptibility to at least one echinocandin, while the remaining nine (69%) were susceptible to all echinocandins, by using the most recent CLSI interpretive breakpoints [11].

Treatment

The most common treatment strategy after diagnosis of candidaemia was initiation of antifungal therapy in patients not receiving antifungal agents (45%) or switching to another class of antifungals in cases of breakthrough infection (17.5%). Other options included addition of antifungal agents to an existing regimen (20%) and continuation of the initial antifungal therapy (15%) (Table 2).

All CVCs were non-tunnelled and were inserted into the subclavian vein. CVCs were removed within 3 days from the onset of candidaemia in 11 patients (27.5%). Median duration of treatment was 12 days (1–81 days) (Table 2). Follow-up cultures were performed in 32 of 40 candidaemia cases. Treatment resulted in negative blood cultures in 28 (86%) of 32 patients, with a median time period to negativity of 8 days (range 1–20 days).

Outcome

Crude mortality in patients with candidaemia and haematological malignancies at day 28 was significantly higher (18 deaths, 45%) compared with control patients (9 deaths, 11%) ($p < 0.0001$) (Fig. 1). Early mortality was 17.5% at day 7 and 30% at day 14. Rates of clinical and mycological response to antifungal therapy at day 7 following the index blood culture for *Candida* were 35% and 47.5%, respectively. Overall response (clinical and mycological) was 42.5% at day 14 and 55% at day 28.

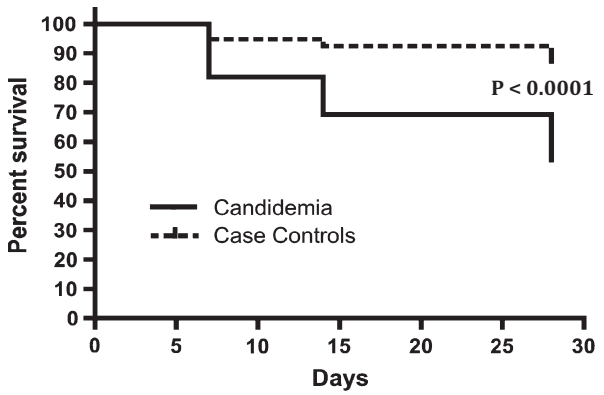

FIG. 1. Kaplan–Meier plot of survival in patients with haematological malignancies and candidaemia vs. case controls with haematological malignancies without candidaemia.

Eleven of the 18 deaths that occurred among case patients were characterized as *Candida* related. Five (45%) of these 11 deaths occurred by day 7 and seven (64%) were attributed to septic shock. Among the *Candida* spp., *C. glabrata* was associated with the highest crude mortality rate (4/4) at day 28, while the lowest mortality was observed in *C. parapsilosis* (6/20) (p 0.008).

Multivariate analysis showed that high APACHE II score (p 0.014; OR, 0.28 (95% CI, 0.06, 0.50)) was an independent risk factor for 28-day mortality among case patients with candidaemia, while neutrophil recovery was associated independently with a favourable outcome [p 0.004; OR, −3.25 (95% CI, −5.74, −1.04)] (Table 3).

Discussion

To our knowledge, this is the first prospective, multicentre study specifically designed to investigate the epidemiology, risk factors and outcome of candidaemia among hospitalized patients with haematological malignancies. We found that the incidence of candidaemia was significantly higher among these patients in comparison to non-haematology patients. Independent risk factors for the development of candidaemia were the presence of CVC, hypogammaglobulinaemia and high APACHE II score. Most infections (87.5%) were due to non-*C. albicans* species, with *C. parapsilosis* being the most common. Twenty-eight-day crude mortality was 45%, with an elevated APACHE II score being an independent risk factor for death; however, recovery from neutropenia was independently associated with improved survival.

TABLE 3. Factors associated with crude mortality at day 28, among 40 case patients

Variable	Bivariate analysis[a] p value	Multivariate analysis OR (95% CI)	p value
Age >50	0.013	2.2 (−0.74, 5.3)	0.14
Neutrophils <100/mL	1.0		
APACHE II score	0.0001	0.28 (0.06, 0.50)	0.014
ECOG score	0.0003		
Breakthrough infection	0.2		
Neutrophil recovery	0.001	−3.25 (−5.47, −1.04)	0.004
Early (<72 h) CVC removal	0.073		
New antifungal therapy	0.022		
Intercurrent bacterial infection	0.31		
Prior use of antibiotics	0.11		

APACHE II, Acute Physiology and Chronic Health Evaluation II; ECOG, Eastern Cooperative Oncology Group; CVC, central venous catheter.
[a]Fisher's exact test was used for categorical variables. The Wilcoxon rank-sum test was used for continuous variables.

The incidence of candidaemia during the 3-year study period was 1.4 cases per 1000 admissions in haematology and/or HSCT units. Although the incidence of candidaemia varies greatly among different hospitals, countries and geographical areas, similar incidences have been reported in European and US studies [1,3,12]. In the 1980s, invasive candidiasis emerged as the prominent mycosis in patients with haematological malignancies. However, following widespread use of antifungal triazole prophylaxis in the early 1990s in leukaemia units, candidiasis has become less common [13]. There also has been an expanded use of echinocandins for prevention and empirical antifungal therapy of invasive candidiasis in neutropenic patients, which may exert a selective microbiological effect on *C. parapsilosis* in this population [14]. Despite these preventive measures in patients with haematological malignancies, we found that the incidence of candidaemia among patients with haematological malignancies was significantly higher compared with that of non-haematological adult patients admitted during the study period. These data suggest that haematological malignancy *per se* is a risk factor for hospital-acquired candidaemia.

We found that hypogammaglobulinaemia was an independent risk factor for development of candidaemia among patients with haematological malignancies. Hypogammaglobulinaemia has not been reported previously as a risk factor for candidaemia in haematological malignancies. This novel observation carries important implications for pathogenesis of the disease, host defence mechanisms and immunotherapy. Although polymorphonuclear leukocytes are the primary line of innate host defence against deeply invasive *Candida* infections, the antibodies also have a key role in protection against disseminated candidiasis. Pooled rabbit anti-Hyr1p polyclonal antibodies raised against eight different peptide regions of rHyr1p-N (*C. albicans* cell surface protein phagocyte killing resistance factor) protected mice in a haematogenously disseminated candidiasis model [15]. That antibodies specific for *C. albicans* cell surface (1→2)-β-mannotriose [β-(Man)$_3$] protect mice from disseminated candidiasis [16] further

supports the role of antibodies in host defence and possible immunotherapeutics. The antibody titre threshold against the N-terminus of the candidal adhesin, Als3p (rAls3p-N), predicts anti-*Candida* vaccine efficacy in the prevention of disseminated candidiasis, despite the mechanism of protection being induction of cell-mediated immunity [17]. Thus, hypogammaglobulinaemia in patients with haematological malignancies may be an important biomarker for the risk of disseminated candidiasis and further provide a rationale for vaccine therapy.

Another independent risk factor for the development of candidaemia was an APACHE II score of ≥20. APACHE II score has not been validated outside the ICU; however, it has been used extensively in published candidaemia studies [18]. Previous studies have shown that increased APACHE II score at the onset of candidaemia is a clinical predictor for progression to septic shock [19] and is independently associated with higher hospital mortality [18,20]. This finding carries several important implications for patients with haematological malignancies. First, sepsis syndrome and elevation of APACHE score may be the first manifestation of candidaemia [19]. Second, rapid intervention with antifungal therapy at this stage may be life-saving [21]. Third, candidaemia also may be a surrogate marker of severe illness and debilitation in patients with haematological malignancies.

Our study demonstrated a striking epidemiological prevalence of 87.5% non-*C. albicans* isolates among patients with haematological malignancies and candidaemia. Whereas older studies attributed such shifts towards non-*C. albicans* spp. to widespread prophylactic use of fluconazole in haematology units [22], in our study only 12/40 patients (30%) were receiving a triazole at the onset of candidaemia. Recent studies showed that in some centres a decline in fluconazole usage did not influence the non-*C. albicans* spp. predominance [22] or that fluconazole prophylaxis was not associated with a shift towards non-*C. albicans* spp. [23]. Other factors, such as broad-spectrum antibiotics and chemotherapy, might also contribute to this trend [24]. We found that non-*albicans* candidaemia was significantly more frequent in patients with haematological malignancies compared with non-haematology patients within the same hospital for the same time period. This finding suggests that patients with haematological malignancies have a distinct *Candida* epidemiology, not associated with local epidemiology or hospital-associated factors.

The preponderance of *C. parapsilosis* in our study is distinct from most reports of non-*C. albicans* spp. in patients with haematological malignancies, in whom *C. glabrata* and *Candida krusei* are most common. However, a retrospective study at the M.D. Anderson Cancer Center showed that *C. parapsilosis* was the most common species among patients with haematological malignancies, during the period 2001–2007 [3]. The decline in fluconazole or itraconazole usage in favour of echinocandins and voriconazole as prophylactic agents may have contributed to this epidemiological change. Echinocandins have elevated MICs against *C. parapsilosis*, which may be correlated with refractory candidaemia or breakthrough infections [25]. Other *Candida* spp., including *C. glabrata, C. tropicalis* and *C. krusei*, also may emerge as resistant isolates during echinocandin therapy [26,27]. A recent study showed significant correlation between increased caspofungin usage and increased incidence of *C. parapsilosis* candidaemia [28]. In our study, only two case patients were receiving an echinocandin at the onset of candidaemia. The prevalence of *non-C. albicans* species, especially *C. parapsilosis*, despite the low percentage of patients receiving prophylaxis suggests that the prior use of antifungal agents is not the only driving force in the shift in distribution of *Candida* species among patients with haematological malignancies. The 2009 IDSA guidelines recommend empirical treatment of neutropenic patients with suspected candidaemia [29]. However, as observed in this study, breakthrough candidaemia with *C. parapsilosis* may develop during neutropenia, possibly in relation to the high MICs of echinocandins.

Our study introduces an important observation of a relatively high proportion (50%) of CVC-related candidaemia episodes. That *C. parapsilosis*, which is strongly associated with vascular catheter infections, also was found in this same cohort, suggests an evolution of candidaemia toward CVCs as a portal of entry. In previous studies, CVCs were considered to be uncommon sources of breakthrough fungaemia in haematological malignancy patients, with the understanding that the alimentary tract was the principal portal of entry for candidaemia in neutropenic hosts [30]. However, *C. parapsilosis* is known to adhere to the surface of CVCs through biofilm formation and thus cause candidaemia [31]. Identification of CVCs as an independent risk factor for the development of candidaemia further substantiates their relationship with *C. parapsilosis* as an emerging pathogen in patients with haematological malignancies.

The high rate of *C. parapsilosis* candidaemia and CVC-related infections might suggest poor hand hygiene standards of healthcare workers because *C. parapsilosis* is a common skin saprophyte [32]. Yet, in the non-haematology patients of our study, treated in the same hospitals for the same time period, the frequency of *C. parapsilosis* was lower. If we take into consideration that hand hygiene policies are usually stricter in haematology units, and that *C. parapsilosis* also was the predominant *Candida* species among haematology patients in a USA-based hospital [3], then transmission of *C. parapsilosis* by the personnel is a less rational explanation. One may hypothesize that *C. parapsilosis* in some patients with haematological malignancies may originate from their own

endogenous cutaneous biome in the setting of expanded use of echinocandins.

We found that among patients with haematological malignancies and candidaemia the overall mortality at day 28 was 45%, and the *Candida*-related mortality was 27.5%. Crude mortality was significantly higher compared with controls (45% vs. 11%, p <0.001; excess mortality, 34%). Similarly high crude and attributable mortality rates among patients with haematological malignancies have been reported in previous retrospective studies from Europe and the USA [2,3,33]. The poor outcome of our study patients, along with the poor clinical and mycological response to antifungal therapy at day 7 (35% and 47.5%, respectively), suggests that candidaemia in patients with haematological malignancies is an ominous sign irrespective of antifungal treatment.

This study had limitations. Our data do not exclude the possibility that the observed incidence of candidaemia is an underestimation of the real incidence because autopsies were not performed in the participating centres. Despite important technological advances in blood cultures [34], *post-mortem* studies demonstrate that they remain insensitive in detecting *ante-mortem* deep tissue candidiasis, especially among patients with haematological malignancies who were receiving antifungal prophylaxis [35]. Secondly, we had a limited absolute number of case patients, due to the relatively low incidence of candidaemia, which did not allow assessment of other potentially important parameters for candidaemia or candidaemia-related mortality. Finally, only Greek hospitals participated in the study; therefore, generalization of our findings to other geographical areas may not be feasible. On the other hand, to our knowledge this is the first multicentre, prospective study on candidaemia among patients with haematological malignancies, without the shortcomings of retrospective, single-centre studies.

In conclusion, this multicentre, prospective study showed that the epidemiology of candidaemia in high-risk patients with haematological malignancies is a continually evolving challenge with regard to successful outcome. Our study adds CVC and hypogammaglobulinaemia as new independent risk factors for candidaemia in patients with haematological malignancies. We found a predominance of non-*C. albicans* isolates, especially *C. parapsilosis*, frequently resistant to at least one antifungal agent. Therefore, defining the optimal management in this high-risk patient population, which typically is not included in candidaemia trials, still remains a major challenge.

Authorship/Contributions

NVS was the principal investigator and takes primary responsibility for the paper. MNG, MP, MK, AS, AM, PO, DK, AP, DS, PM and GD recruited the patients. MNG, AA, SP and IS performed the laboratory work for this study. TZ, KL and TJW performed the statistical analysis. MNG, GP and NVS coordinated the research. MNG, TJW and NVS wrote the paper.

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Transparency Declaration

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